IN THE UNITED STATES PATENT OFFICE

Application serial No. 10/083,529 Docket no. UND-99-02-D1

Applicant: Undurti Narasimha Das Primary Examiner: Pryor, Alton Nathaniel

Title: A method of stabilizing and potentiating the action of anti-angiogenic substances

Group Art Unit: 1616

Response to the Office Action mailed on 12/31/2007

This is a response to the Office Action mailed on 12/31/2007, for which the 3 month(s) deadline falls on 03/30/2008. At the outset, the examiner is thanked for his response and for the telephonic conversation on 04 March 2008.

During this telephonic conversation the following aspects of the pending application were discussed:

1. The examiner wanted an explanation about the words "causing antiangiogenic action" used in claim 2 of the application. The examiner felt that these words are not clear, based on which the claim 2 was rejected in the office action of 12/31/2007.
2. The examiner opined that claim 3, lines 3-4 reciting: "antiangiogenic substance is to the extent of 1 to 1000 mg/kg" is not clear and wanted to have a clarification of the same.
3. The examiner also wanted to know how the claims 1 and 3 are distinct from the work of Yanai et al (Pharmaceutical Research 1995, 12 no.5, pages 653-657) and Kokura et al (Cancer Research 1997, 57 no. 11, pages 2200-2202). Yanai et al described treating a tumor comprising an intra-arterial injection of an angiogenesis inhibitor (TNP-470), whereas Kokura et al described a method of treating a tumor comprising an intra-arterial injection of alpha-linolenic acid. Based on these descriptions, the examiner opined that it would have been obvious to combine the two actives (angiogenesis inhibitor and fatty acid component) for the utility of treating tumor.
4. The examiner suggested that claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 12-18 of U.S. patent No. 6426367. Although the examiner accepted that the scope of two inventions (U.S. patent no. 6426367 and the pending application 10/083, 529) differ, the combination of the two groups of claims makes obvious the claims in instant application

where the independent claims alone disclose the combination of the fatty acid and anticancer agent (angiogenic substance) being injected into the artery. At this instance the inventor (U N Das) disagreed with the opinion of the examiner that anticancer and antiangiogenic substances are same. The inventor feels that anticancer and antiangiogenic substances are two different entities and hence these two terms cannot be used interchangeably. At this instance, the examiner wanted the inventor (U N Das) to present evidence from the literature that these two substances (i.e. anticancer and antiangiogenic substances) are different.

5. The examiner opined that the inventor (U N Das) may opt to file a terminal disclaimer with regard to the patent no. 6426367.

The inventor (U N Das) during the telephonic conversation with the examiner respectfully disagreed with the observations made by the examiner (points 1-5 described above). As desired by the examiner, the inventor (U N Das) wishes to present point by point rebuttal and explanations in support of the claims 1-7 made in the pending application no. 10/083,529 (UND-99-02-D1) and are given below:

1. **Explanation about the words: "causing antiangiogenic action":** On page 2, under the heading "Background of the Invention", paragraph 0007, starting from the first line a definition of the term angiogenesis has been described. This is extracted here for easy reference. The sentence reads as follows: "The term angiogenesis refers to the generation or formation of new blood vessels into a tissue or organ. Angiogenesis can occur both during physiological processes and/or in some pathological conditions. For example, angiogenesis can be seen to occur during wound healing, fetal growth, corpus luteum, and endometrium, etc., (1). Endothelial cells, which cause to form the inner lining of the blood vessels, are constituted by a thin layer of epithelial cells and these cells are necessary for the process of angiogenesis. During the process of angiogenesis, irrespective of whether it is physiological or pathological, the endothelial cells release enzymes which can produce erosions of the basement membrane through which the endothelial cells cause protrusions. In response to the stimuli given by various agents, endothelial cells proliferate and migrate through the protrusions and form a sprout of the

parent blood vessel. These endothelial cell sprouts can merge to form capillary loops leading to the formation of new blood vessel(s)".

Reference 1. Battegay EJ. Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects. J Mol Med 1995; 73: 333-346.

Thus, it is seen that in this section of the text of the patent application, the inventor (U N Das) has clearly described the meaning of the word angiogenesis and the mechanism of its formation with a reference to an article published in the journal: Journal of Molecular Medicine. It is evident from this description that angiogenesis is a process of formation of new blood vessels and that the mechanism of angiogenesis process involves proliferation of endothelial cells, their migration, formation of sprouts from the parent blood vessel and finally leading to the formation of new blood vessels. It is obvious from this description that antiangiogenesis process is opposite of this. In other words, antiangiogenesis means inhibition of endothelial cell proliferation, and prevention of formation of new blood vessels and collaterals.

On page 10, paragraphs 0033, the following sentences (starting from 2nd sentence in this paragraph) have been given that clearly describe the meaning of the words: "causing antiangiogenic action". The extracted sentence is as follows: "The invention also provides a method of causing anti-angiogenic action in the tumor region with the result that new blood vessels and collaterals are not formed to sustain the tumor".

On page 11, paragraph 0034, starting from the first sentence again the meaning of the words "causing antiangiogenic action" has been clearly explained. The extracted sentences from the text is given here: "The invention in yet another aspect teaches a method of interrupting blood using a pre-determined admixture of at least a PUFA and an anti-angiogenic agent causing necrosis with very desirable results. Both the PUFAs and anti-angiogenic compounds being similar in function, the invention also provides a method of causing anti-angiogenic action in the tumor region with the result that new blood vessels and collaterals are not formed to sustain the tumor in the tumor region treated according to the invention".

The extracted sentences from the text of the patent application explain the meaning of the word angiogenesis as generation or formation of new blood vessels, whereas "causing antiangiogenic action" means "inhibiting endothelial cell proliferation and causing an action where new blood vessels and collaterals are not formed".

In the website of American Cancer Society the meaning of the word angiogenesis and anti-angiogenesis is given as follows:

What Is Anti-angiogenesis Treatment?

Angiogenesis is the creation of new blood vessels. The term comes from 2 Greek words: **angio**, meaning "blood vessel," and **genesis**, meaning "beginning."

Normally, this is a healthy process. As the human body grows and develops, it needs to make new blood vessels to get blood to all of its cells. As adults, we don't have quite the same need for making new blood vessels, but there are times when angiogenesis is still important. New blood vessels, for instance, help the body heal wounds and repair damaged body tissues.

But in a person with cancer, this same process creates new, very small blood vessels that provide a tumor with its own blood supply and allow it to grow.

Anti-angiogenesis is a form of targeted therapy that uses drugs or other substances to stop tumors from making new blood vessels. Without a blood supply, tumors can't grow.

2. **The examiner opined that claim 3, lines 3-4 reciting: "antiangiogenic substance is to the extent of 1 to 1000 mg/kg" is not clear and wanted to have a clarification of the same.**

The examiner wanted the inventor (U N Das) to explain this sentence as it is not clear. On page 19, under paragraph 0057 and line 6, in the text of the patent application it has been stated as follows: "The PUFAs may be provided in a daily dose of 0.5 mg to 50 gm together with appropriate doses of conventional anti-cancer drugs such as vincristine, L-asparaginase, cis-platinum, busulfan, etc., in a daily/weekly/monthly dose of 1 mg to 50 gm depending on the requirement and the stage of the disease and as may be determined from time to time with or without the addition of anti-angiogenic protein/peptide such as Angiostatin/endostatin in a dose of 1 mg to 100 mg/kg of body weight per day".

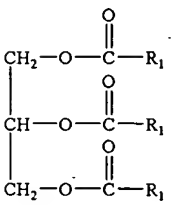
Hence, the inventor (U N Das) would like to clarify the claim 3 lines 3-4 recited "antiangiogenic substance is to the extent of 1 to 1000 mg/kg" as meaning: "antiangiogenic substance is provided in a dose of 1 to 1000 mg/kg".

In view of this and in order to make the claim clearer, the inventor (U N Das) would like to seek the permission of the examiner to amend the claim 3 as follows: "antiangiogenic substance is provided in a dose of 1 to 1000 mg/kg/body weight".

3. **The examiner also wanted to know how the claims 1 and 3 are distinct from the work of Yanai et al (Pharmaceutical Research 1995, 12 no.5, pages 653-657) and Kokura et al (Cancer Research 1997, 57 no. 11, pages 2200-2202). Yanai et al described treating a tumor comprising an intra-arterial injection of an angiogenesis inhibitor (TNP-470), whereas Kokura et al described a method of treating a tumor comprising an intra-arterial injection of alpha-linolenic acid. Based on these descriptions, the examiner opined that it would have been obvious to combine the two actives (angiogenesis inhibitor and fatty acid component) for the utility of treating tumor.**

Yanai et al in their publication in the journal Pharmaceutical Research 1995 May; 12(5): pages 653-657 described the antitumor activity of a medium-chain triglyceride (MCT) solution of an angiogenesis inhibitor, TNP-470 (AGM-1470, 6-O-(N-chloroacetylcarbamoyl)-fumagillol), following administration into the femoral artery feeding the tumor that is situated on the inner side of the leg.

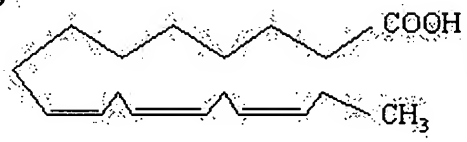
The inventor (U N Das) would like to mention here that medium-chain triglycerides are totally different from polyunsaturated fatty acids both structurally and functionally. The structure of a medium-chain triglyceride is given below:



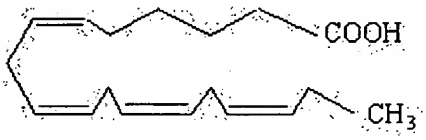
Medium chain triglycerides (MCT) commonly abbreviated MCT or MCTs, are medium-chain (6 to 12 carbons) fatty acid esters of glycerol. MCTs passively diffuse from the GI tract to the portal system (longer fatty acids are absorbed into the lymphatic system) without requirement for modification like long chain fatty acids or very long chain fatty acids do. In addition MCTs do not require bile salts for digestion. Patients who have malnutrition or malabsorption syndromes are treated with MCTs because they do not require energy for absorption, utilization, or storage. Rich sources of MCTs include coconut oil and palm kernel oils and are also found in camphor tree drupes. The fatty acids found in MCTs are called medium chain fatty acids. The names of the medium chain fatty acids (and the corresponding number of carbons) found in MCTs are: caproic (C6), caprylic (C8), capric (C10) and lauric acid (C12). MCTs are composed of a glycerol backbone and three of these fatty acids. The approximate ratios of these fatty acids in commercial MCT products derived from coconut oil is 2(C6):55(C8):42(C10):1(C12).

These MCTs are different from PUFAs (polyunsaturated fatty acids described in the pending patent application of the inventor (U N Das). The structure of some of the PUFAs is given below:

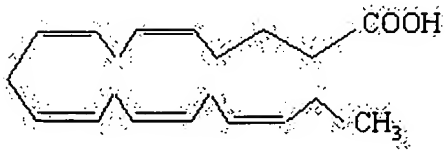
(a)



(18:3ω3; 18:3n3; 18Δ9,12,15)
(α-linolenic acid, ALA)



(18:4ω3; 18:4n3; 18Δ6,9,12,15)
(stearidonic acid, SA)



(20:5ω3; 20:5n3; 20Δ5,8,11,14,17)
(eicosapentaenoic acid, EPA)

(22:6ω3; 22:6n3; 22Δ4,7,10,13,16,19)
(docosahexaenoic acid, DHA)

Thus, it can be seen that the structure of PUFAs is different from those of MCTs. MCTs contain fatty acids that are only 6 to 12 carbons long whereas PUFAs contain fatty acids that contain carbons anywhere from 18 to 22. Furthermore, MCTs contain a glycerol molecule in its structure whereas glycerol is not present in PUFAs.

In addition, in the work described by Yanai et al there is no description of blocking of blood supply to the tumor, whereas in the present invention the inventor observed inhibition of

blood supply to the tumor (see under Summary of invention: page 10, paragraph 0031, lines 6-9). The actual description given in these sentences in the text of the patent application is given below for easy reference:

"In this context, it is important to note that the inventor has found that polyunsaturated fatty acids (PUFAs) such as gamma-linolenic acid (GLA), dihomo-GLA (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can selectively kill the tumor cells (27-32) and under specific conditions and in conjugation with salts such as lithium and a lymphographic agent these fatty acids can actually behave as antiangiogenic substances, i.e. they block all the blood supply to the tumor and also prevent generation of new blood vessels. Using these fatty acids in this particular combination, the inventor has successfully treated human hepatocellular carcinoma and giant cell tumor of bone with few or no side-effects".

Yanai et al in their study described regression of tumor by their method of intra-arterial injection but never mentioned anywhere in their publication any block of blood supply to the tumor. Thus the invention of the inventor (U N Das) is clearly distinct from that of Yanai et al in that there is complete block of the blood vessels feeding the tumor.

For easy reference, please find enclosed the abstract of the publication of Yanai et al (Annexure 2).

Based on these observation, the inventor (U N Das) wishes to emphasize that the observations made by Yanai et al is different from that made by the inventor (U N Das)-

Yanai et al did not report any blocking of blood vessels feeding the tumor whereas the inventor (U N Das) observed blocking of the blood vessels feeding the tumor-which is a novel and hitherto unknown observation.

With regard to the work of Kokura et al published in Cancer Research 1997 June 1; 57 (11): pages 2200-2202, who described that oleic acid, linolenic acid, alpha-linolenic acid, or gamma-linolenic acid was injected into the arteries feeding AH109A carcinoma implanted into rat hind limbs when combined with hyperthermia particularly, wherein gamma-linolenic acid injection into the feeding artery of a tumor was performed immediately prior to hyperthermia

observed a significant antitumor effect due to a high level of lipid peroxidation. But, in their publication, Kokura et al (see Annexure-3 an abstract of the paper by Kokura et al) did not report any blocking of neither tumor feeding blood vessels nor anti-angiogenic action. This again is different from the observations made by the inventor (U N Das) since the inventor specifically observed interrupting blood supply to a tumor region causing necrosis or apoptosis. For easy reference, please find given below the relevant extract from the text of the patent application (see under Summary of invention: page 10, paragraph 0031, lines 6-9):

"In this context, it is important to note that the inventor has found that polyunsaturated fatty acids (PUFAs) such as gamma-linolenic acid (GLA), dihomo-GLA (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can selectively kill the tumor cells (27-32) and under specific conditions and in conjugation with salts such as lithium and a lymphographic agent these fatty acids can actually behave as antiangiogenic substances, i.e. they block all the blood supply to the tumor and also prevent generation of new blood vessels. Using these fatty acids in this particular combination, the inventor has successfully treated human hepatocellular carcinoma and giant cell tumor of bone with few or no side-effects".

In view of the above facts, the inventor (U N Das) respectfully disagrees with the examiner and suggests that the work of Yanai et al and Kokura et al is different from that of the inventor (U N Das). Hence, the inventor wishes to request the examiner to withdraw the rejection of the claims 1-3.

4 **The examiner suggested that claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 12-18 of U.S. patent No. 6426367. Although the examiner accepted that the scope of two inventions (U.S. patent no. 6426367 and the pending application 10/083, 529) differ, the combination of the two groups of claims makes obvious the claims in instant application where the independent claims alone disclose the combination of the fatty acid and anticancer agent (angiogenic substance) being injected into the artery. At this instance the inventor (U N Das) disagreed with the opinion of the examiner that anticancer and antiangiogenic substances are same. The inventor feels that anticancer and antiangiogenic substances are two different entities and hence these**

two terms cannot be used interchangeably. At this instance, the examiner wanted the inventor (U N Das) to present evidence from the literature that these two substances (i.e. anticancer and antiangiogenic substances) are different.

There are distinct differences between classical anti-cancer drugs such as vincristine, doxorubicin, cis-platinum, and adriamycin that do not have ant-angiogenic action and anti-angiogenic drugs. These anti-cancer drugs directly act on the cancer cells, inhibit their proliferation and kill them. On the other hand, anti-angiogenic substances do not have any direct action on tumor cells but by blocking or decreasing blood supply to tumor induce regression of tumor. Thus, anti-cancer drugs have a direct action on cancer cells whereas anti-angiogenic drugs have action on blood vessels that feed the tumor. In the case of anti-cancer drugs, regression of tumor growth may cause a decrease in the amount of blood flowing to the tumor. But, this is a consequence of tumor regression but not as a result of direct action of anti-cancer drugs on blood vessels that are feeding the tumor. Thus, by convention anti-angiogenic drugs are also called as anti-cancer substances whereas anti-cancer drugs are not labeled as anti-angiogenic drugs.

In this context, the inventor (U N Das) performed a thorough Medline search using the search words: anti-cancer drugs as anti-angiogenic substances (see Annexure-4), and anti-cancer drugs in angiogenesis which revealed that there are 12 papers in this field. None of these 12 papers mentioned that anti-cancer drugs can have antiangiogenic action. This indicates that conventional anticancer drugs such as vincristine, doxorubicin, adriamycin, and cis-platinum do not have any antiangiogenic action by themselves.

In contrast to this, antiangiogenic substances are also designated as anti-cancer drugs. This is so since when antiangiogenic drugs or substances are given they regress cancer by reducing blood supply to the tumor area. But, it should be noted that antiangiogenic drugs or substances do not have any action on tumor cells directly. This, anti-cancer drugs and antiangiogenic drugs are distinctly different and so anticancer drugs cannot be called as antiangiogenic drugs and at the same time antiangiogenic drugs cannot be strictly called as

anticancer drugs but do show anticancer action by virtue of their ability to decrease tumor size by decreasing blood supply to the tumor.

Another objection raised by the examiner is the nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 12-18 of U.S. patent no. 6426367. The examiner agreed that although the conflicting claims are not identical, they are not patentably distinct from each other because in claims 1-6, 12-15 one group) of USPN '367 is disclosed a method of intra-arterially injecting polyunsaturated fatty acids (the Li salt as well) into an artery and in claims 16-18 (another group) of USPN '367 is disclosed a method of further comprising injecting an anticancer agent into the artery. The combination of the claimed groups in USPN '367 suggests the instant claims. Further, the examiner agreed that although the scope of the two inventions differ, the combination of the two groups of claims makes obvious the claims in instant application where the independent claims alone disclose the combination of the fatty acid and anticancer agent (angiogenic substance) being injected into the artery.

The inventor (U N Das) wishes to respectfully disagree with the examiner on this point. In the U.S. patent no. 6426367, in the claims 1-6 and 12-15 there is indeed a mention of intra-arterial injection of polyunsaturated fatty acid (in claims 1-6 and 12-15) and using in conjunction with tumor necrosis factor, an anticancer drug, a lymphokine and specific polyclonal and monoclonal antibodies (claim 16) and covalently conjugated to a pharmaceutical agent chosen from the group consisting of vincristine, doxorubicin, cyclophosphamide, cis-platinum, L-asparaginase, procarbazine, camptothecin, taxol, and busulfan, which are all anticancer drugs (claim 18). On the other hand, in the pending patent application in claim 4 antiangiogenic substances chosen are: platelet factor-4, TNP-470, thalidomide, interleukin-12, and metalloprotease inhibitors and a predetermined anticancer drug. Thus, this claim is distinctly different from the claims made in the US patent no. 6426367. Furthermore, in claim 5 a-d of the pending patent application there is mention of obtaining an initial radiographic image of the tumor region (see claim 5b) and obtaining a second and subsequent radiographic images of the tumor after predetermined lapses of time (see claim 5d) and comparing the initial radiographic image with the second and subsequent images to assess an extent of remission of the tumor (see

claim 5e). This claim 5 is distinctly different from the claims 12-15 of the U.S. patent no.6426367.

Thus, in the U.S. patent no. 6426367, the claims are in conjunction with PUFAs and anticancer drugs, whereas in the pending patent application the claims are in conjunction with PUFAs and antiangiogenic substances. As already discussed above, anticancer drugs are different from antiangiogenic substances. Furthermore, in the pending patent application there is a mention of taking initial and later radiographic images to assess the extent of remission of the tumor whereas this is not so in the U. S. patent no. 6426367.

As suggested by the examiner, to overcome this problem of nonstatutory obviousness-type double patenting, the inventor (U N Das) is here with submitting the duly filled in and signed terminal disclaimer.

I may add here that terminal disclaimer was already filed on August 11, 2007 along with a fee of US$ 65 by Mr. Ram Nath, my previous attorney. A copy of the check of US$65 that was paid in this context is here with enclosed. However, I am enclosing another terminal disclaimer signed by me for your records.

In view of the explanations offered above to various objections raised by the examiner, I would like to request that the rejection of the claims 1-7 may be set aside and accept the claims at an early date.

For easy reference, I am here with enclosing the claims 1-7 with minor modifications in the claim 2.with regard to the dose of the fatty acid to be used.

I may also bring to the kind attention of the examiner that this patent application has been pending since 02/27/2002 and hence, an early issue of the patent will be greatly appreciated.

With regards,

Sincerely,

Undurti N Das.

Date: 20th March 2008.